REMARKS

FORMAL MATTERS

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 are pending after entry of the amendments set forth herein.

Claims 6, 7, 9, 11-12, 21, 23-26, 29, 36-39 and 41 are canceled without prejudice. Applicant expressly reserves the right to pursue the subject matter of these claims in a continuing application.

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 are amended. The Applicant has amended the dependent claims to begin with "The" in order to correct for form. The Applicant has amended the claims to specify the term "rodent." Support for this term is found in the specification, for example, beginning at page 18, line 34 and continuing to page 19, line 4.

No new matter is added.

OBJECTIONS TO THE CLAIMS

The Examiner objected to the dependent claims for recitation of "A" rather than "The". The Examiner is thanked for pointing this out, and the claims are amended to address this objection. Withdrawal of this objection is respectfully requested.

THE REJECTION UNDER 35 U.S.C. §101

The Examiner has rejected claims 1-5, 8, 10, 12-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. §101 as allegedly lacking in patentable utility. The Applicant respectfully traverses the rejection.

The requirement of utility derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966), holding that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In addition, the M.P.E.P. has provided significant guidance to Examiners in determining substantial utility for research tools in §2107.01(1)(c): "Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are

useful in analyzing compounds)" a standard that is alluded to by the Examiner in the Office Action.

The Applicant asserts that the utility requirement is fulfilled and have asserted that the invention can be used in screening and analyzing candidate compounds. Applicant addresses the Examiner's assertions, and provide support for arguments in rebuttal, below.

The role of C5a/C5aR

The Examiner asserts that the specification and the art at the time of filing do not disclose any disease affected by C5a binding to C5aR.

Contrary to the Examiner's assertion, at the time of filing it was known that C5a is a very potent inflammatory molecular that mediates its effects by binding to its receptor C5aR. C5a binding to C5aR causes migration of neutrophils, and promotes activation and release of destructive enzymes and other pro-inflammatory molecules. If this process is uncontrolled, then the inflammatory reaction can damage surrounding tissues. Certain diseases and inflammatory conditions are considered to be the result of uncontrolled C5a/C5aR signaling. Moreover, at the time of filing it was known that blocking C5a/C5aR signaling using C5a or C5aR antagonists would ameliorate disease in animal models of chronic and acute inflammatory disease (e.g., Kohl (2001), *Mol. Immunol.* 38:175-187, of record).

Moreover, the specification explicitly describes use of the claimed invention in this context. For example, at page 7, line 23 to 30, the specification states:

> It will be appreciated that the transgenic mammals of the present invention will be useful in the identification, evaluation or validation of novel agonists, inverse agonists and antagonists of C5aR. For example, transgenic mammals of the present invention can be used to screen a number of candidate compounds to identify agonists, inverse agonists or antagonists of human C5aR function. The transgenic mammals of the present invention can also be used to evaluate the therapeutic suitability of agonists, inverse agonists or antagonists of human C5aR function that have previously been identified in screening methods.

The specification also describes disease states affected by C5aR signaling an din particular the potential uses of agonists and antagonists of C5aR. For example, at page 2lines 9 to 18, the specification states:

> Agonists of C5aR are useful for therapeutic purposes, for example, in defence against bacterial infection, to stimulate immunoregulatory effects of C5a, and to treat cancers, immunodeficiency diseases and severe infections.
>
> Antagonists of C5aR are also useful therapeutic agents, for example for treating inflammatory diseases and autoimmune disorders. For example, antagonists of C5aR are useful in the treatment of asthma, bronchial allergy, chronic inflammation, systemic lupus erythematosis, vasculitis, rheumatoid arthritis, osteoarthritis, gout, some auto-allergic diseases, transplant rejection, inflammatory bowel disease (for example, ulcerative colitis), in certain shock states, myocardial infarction, and post-viral encephalopathies. To this end, C5aR peptide antagonists and anti-C5a receptor antibodies have been previously described. For example, WO95/00164 describes antibodies directed against an N-terminal peptide (residues 9-29) of the C5a receptor.

Phenotypes (or specific disorders) associated with C5aR signaling are also discussed in detail in the specification at page 37, line 33 through page 44, line 12.

The specification thus describes a utility of the claimed transgenic animals, namely the use of the transgenic animals in the identification, evaluation and/or validation of agnostic inverse agonists and antagonists of C5aR.

Use of the claimed transgenic animals as models of disease

The Examiner further asserts that the claimed transgenic animals are not models for disease because they do not have mutated C5aR, and further the specification does not teach that transgenic animals expressing normal human C5aR correlate to any disease found in humans.

Contrary to this assertion, Applicant respectfully submits that the claimed transgenic animals do, indeed, work effectively as models for disease.

To aid in the further discussion of evidence of utility as presented in the present application, it is useful to introduce the nomenclature used. The term "H5Rf" for human C5aR

transgenic mice is introduced in Example 3 at page 56, lines 26-27: "The genotype of these mice was designated as hC5aRfloxed(neoR)/wt (abbreviated H5Rf+)." The K/BxN mouse model for rheumatoid arthritis is introduced and made of reference on page 39, lines 18-20. It is further described in Example 6, that K/BxN transgenic mice develop a very aggressive form of arthritis. When serum is taken from K/BxN mice and injected into healthy mice, it induces arthritis in these mice within days. The antibody 7F3 is a C5aR antagonist antibody that is specific to human C5aR, and is discussed in the specification at page 3, lines 21-22.

Example 6 of the specification demonstrates that the H5Rf mice can be used to screen for candidate compounds that modulate the inflammatory response (see pages 59-63), and further can serve as a model of human rheumatoid arthritis.

Specifically, in Example 6, serum from K/BxN mice was administered to H5Rf mice and control mice at day (0) and day (+2), causing inflammation and arthritis as shown in Figure 6. The 7F3 antibody or a control IgG2a antibody were injected into H5Rf mice treated with K/BxN serum at day (-1) and day (+3). H5Rf (Fig. 7, (#10, #25)) mice develop ankle swelling and other signs of inflammation when treated with the control antibody. However, H5Rf mice administered the 7F3 antibody did not develop clinical signs of inflammation, showing a reduction in swelling and inflammation. This result is shown graphically in Figure 7, (#7 and #24), represented by the dashed line and open triangles, respectively. The reduction of inflammation upon administration of the 7F3 anti-human C5aR antibody to the human C5aR knock-in mice is clearly demonstrated. Furthermore, histological analysis revealed that the H5Rf mice injected with 7F3 had no tissue damage when compared to the mice injected with the control antibody. This indicates that that the anti-human C5aR antibody was exerting its antagonistic effect through the knock-in human C5aR gene. Wild type mice (Fig. 7 #38) injected with K/BxN serum and treated with 7F3 antibody show high levels of inflammation similar to mice treated with a control antibody.

Example 6 thus demonstrates the claimed transgenic animals can be used so as to provide a model of human arthritis, e.g., by induction of inflammation by the administration of K/BxN serum. Moreover, the specification shows that this inflammation can be reduced by administration of the 7F3 antibody. This evidence in the specification supports Applicant's

assertion that the claimed transgenic animals can be effectively used in screening for anti-inflammatory drugs. For example, candidate compounds can be administered to H5Rf mice treated with K/BxN serum, and the modulation of inflammation induced by the candidate compound can be compared to the level of inflammation in H5Rf mice treated with the 7F3 antibody. The This use was clearly contemplated as Example 6 concludes: "This data clearly shows that the human C5aR knock-in mice are useful for testing compounds for anti-inflammatory activity in inflammatory disease models" thus confirming the Applicant's assertion that the C5aR knock-in mice have a patentable utility for screening compounds.

Xx The art also recognizes the utility of the C5aR knock-in mice as a screening tool. In the review by Monk et al., which was provided by the Examiner, the conclusion section on page 441 states, at the text bridging the two columns:

Conclusions

There is now strong evidence of a pathogenic role for C5a from studies in numerous disease models using antibodies to C5a or C5aR, soluble receptor sCR1 and C5aR-knockout and knockin transgenic mice (Weisman *et al.*, 1990; Bozic *et al.*, 1996; Goodfellow *et al.*, 1997; Hopken *et al.*, 1997; Mohr *et al.*, 1998; Lee *et al.*, 2006), and especially from studies of small molecule antagonists (for example Table 2).

(emphasis added)

The Lee et al. 2006 reference,[1] which published after the priority date of the present application, is a publication from the present inventors' laboratory describing work with the transgenic animals of the present claims.

[1] Lee H, Zahra D, Vogelzang A, Newton R, Thatcher J, Quan A, So T, Zwirner J, Koentgen F, Padkjaer SB, Mackay F, Whitfeld PL, Mackay CR. (2006) "Human C5aR knock-in mice facilitate the production and assessment of anti-inflammatory monoclonal antibodies." *Nat. Biotech.* 24(10):1279-84. Epub 2006 Sep 17.

Use of the claimed transgenic animals to identify compounds that modulate C5aR-mediated activity

The Examiner asserts that Applicant has left those of ordinary skill in the art with no information on how to use the claimed transgenic animals to identify compounds that target human C5aR. Applicant respectfully disagrees.

As explained above, Example 6 of the specification illustrates that the claimed transgenic animals can be used as a model of human rheumatoid arthritis, and further provides ample guidance on how to carry out such a screening assay and further that one would expect that compounds that modulate C5aR-mediated inflammation in this animal model can be identified. This evidence is sufficient to demonstrate that the claimed transgenic animals have specific and substantial utility that is credible. See MPEP § 2107.

Summary

The specification provides both an explicit asserted utility and data in support of that utility – namely, that the human C5aR knock-in transgenic mice can be used in the screening of compounds, which has a "clear, specific and unquestionable utility" as described in the M.P.E.P. at §2107.01(1)(c). As such, Claims 1-5, 8, 10, 12-20, 22, 27, 28, 30-35 and 40 are supported by a patentable utility. Withdrawal of this rejection is respectfully request.

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected Claims 1-5, 8, 10, 12-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. §112, first paragraph. Each ground of this rejection is addressed below.

First, the Examiner asserts that because the claims are not supported by a patentable utility, that one of skill in the art would not know how to make and use the claimed invention. To the extent the rejection under §112, first paragraph is applied in connection with the utility rejection under §101 discussed above, Applicant submits that he has demonstrated the claims are supported by a patentable utility as discussed above. Because the claimed transgenic mice have a specific and substantial utility that is credible, the claimed transgenic animals also meet the enablement requirement under §112, first paragraph.

Second, the Examiner asserts that upon overcoming the utility rejection, the claims would be subject to rejection under 35 U.S.C. §112, first paragraph, as allegedly not teaching how to make knock-in transgenics in mammals other than mice.

Applicant notes that at the time of filing various transgenic non-human mammals had been produced including, mice, rats, sheep, cots, pigs and goats. However, without agreeing with the grounds of this rejection, and while reserving the right to pursue claims to other transgenic animals in a continuing application, the claims are amended to specify transgenic "rodent" to expedite prosecution. Support for this is found in the specification beginning at page 18, line 34 and continuing to page 19, line 4.

Accordingly, withdrawal of all rejections of the claims under §112, first paragraph is respectfully requested.

THE REJECTION UNDER 35 U.S.C. §103(A)

The Examiner has rejected Claims 1-5, 8, 10, 12-20, 22, 27, 28, 30-35 and 40 under 35 U.S.C. §103(a) as allegedly being obvious over Sato (Thrombosis and Haemostasis (1999) 82(2):865-869- henceforth "Sato"), Roebroek (Methods in Molecular Biology (2003) 209:187-200- henceforth "Roebroek"), Homanics (Methods in Alcohol Related Neuroscience Research (2002), pg 31-61- henceforth "Homanics"), Lester et al, (Curr. Opin. Drug Discov. and Dev. (2003) 6(5):663-639-henceforth "Lester"), Champtiaux (Curr. Drug Targets, CNS & Neuro. Dis.(2002)1:319-330- henceforth "Champtiaux"), Girardi et al., (J.Clin. Invest. (2003) 112(11):1644-1654- henceforth "Girardi") in view of Burmer et al., (WO 02/61087- henceforth "Burmer"). The Applicant respectfully traverses the rejection.

The court in *KSR* held that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions."[2]

[2] In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were taught in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme

As admitted by the Examiner, none of these references teaches a human C5aR knock-in transgenic mouse. The Examiner relies on Girardi, which teaches a knock –out of the mouse C5aR gene in mice and Burmer, which discloses only the human C5aR sequence. The remainder of the references provides background on knock-in technology or knock-ins of other genes than C5aR. From these references the Examiner finds that one of skill in the art would be motivated to replace the mouse C5aR gene with that of the human C5aR gene to test the functional redundancy of the human gene.

The Applicant asserts it would not have been obvious to make a human C5aR knock in mouse, because at the time of filing, the invention is much more than the predictable use of the cited prior art elements of a knockout mouse with no endogenous C5aR expression and the sequence of the human C5aR cDNA. At the priority date of the present application, it was not known or predictable:

- whether mouse C5a, the endogenous ligand, would bind efficiently to the exogenous human C5a receptor ***in vivo*** and activate human C5aR signaling; or
- whether mouse C5a would cause chemotaxis of mouse leukocytes expressing human C5aR.

The amino acid sequence identity between the mouse C5aR and the human C5aR is about 66% overall and 29% identical between the N-terminal and the 2nd extracellular loop, which is responsible for C5a ligand binding (see Appendix A, attached).

Given this low level of amino acid sequence identity, and particularly the low level of sequence identity over the regions that mediate C5a binding, it is not predictable from the cited art whether the endogenous mouse C5a ligand would bind to the knocked-in human C5aR to mediate activation of a human C5aR and further to mediate signaling pathways in the mouse

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Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740; emphasis added . As such, in addition to showing that all elements of a claim were taught in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

cells. Further, one could thus not predict from the cited art whether an inflammatory response could be induced in the claimed transgenic animals by administration of K/BxN serum, and that this inflammatory response could be adequate to serve as a model of human rheumatoid arthritis, as discussed above.

In summary, the generation of a human C5aR knock in mouse and its use in screening candidate compounds cannot be predicted from the cited prior art elements of a murine C5aR knock out mouse which expresses no C5aR and a disclosure of the human C5aR sequence. As such, Claims 1-5, 8,10,12-20, 22, 27, 28, 30-35 and 40 are ***not*** obvious under 35 U.S.C. §103(a), and this rejection may be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-050.

Respectfully submitted,
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Date: March 10, 2009

By: /Carol L. Francis,Reg.No.36513/
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* Enclosure: Appendix A

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